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NEPHROLOGY FORUM

Preventing the progression of human renal disease: Have rational therapeutic principles emerged?

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Case presentation

A 64-year-old Mexican-American woman was referred to the nephrology clinic at UCLA 3.5 years ago, having been followed by an internist for the previous 8 months because of chronic renal failure. Fourteen years ago, the patient was found to have mild hypertension. Four years later, the serum creatinine was 2.4 mg/dl and she had 3+ proteinuria. A renal biopsy was not performed; the diagnosis was presumed to be chronic glomerulonephritis. The patient's history also suggested that she might have gout. She was followed by her referring physician, who documented that her blood pressure was under good control until one month before the detection of advancing renal failure. At that time, blood pressure was 190/98 mm Hg standing and 198/94 mm Hg supine. Hydralazine, 25 mg twice daily, was added to her previous antihypertensive medications, which were propranolol, 80 mg three times daily, and hydrochlorothiazide, 50 mg daily. Serum creatinine was 3.6 mg/dl; urinalysis revealed 2+ protein, 5 to 10 red blood cells/high-power field; and 5 to 10 white blood cells and numerous granular casts/high-power field. Repeated blood pressure measurements over the next few months ranged from 170/72 mm Hg to 180/90 mm Hg. One month prior to referral to UCLA, creatinine clearance was 10 ml/min; serum creatinine, 5.1 mg/dl; and proteinuria, 2.2 g/24 hours.

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When the patient was seen at UCLA, she was taking propranolol, 80 mg four times daily; furosemide, 40 mg/day; minoxidil, 2.5 mg/day; allopurinol, 100 mg/day; ferrous sulfate, 325 mg three times daily; and folic acid, 1 mg/day. On examination she was a pale woman with hair over the back of the arms and on the sides of the face. Blood pressure was 190/100 mm Hg supine and 190/100 mm Hg standing; the pulse was 88 beats/min and regular. Optic fundi showed grade I-II hypertensive retinopathy. Cardiac apex beat was localized to the 5th intercostal space, just inside the anterior axillary line. An S_3 was heard. The lungs were clear. There was no jugular venous distention, hepatomegaly, or edema. Peripheral pulses were intact and symmetrical. Central nervous system examination was normal. Urinalysis showed 2+ protein, and 5 to 10 white blood cells, 5 to 10 red blood cells, and numerous granular casts/high-power field. Minoxidil was increased to 2.5 mg twice daily, and both furosemide and propranolol were continued. The patient was instructed to reduce her protein intake by eliminating meat, fish, eggs, and milk from her diet.

Over a 3-year period, blood pressure was maintained in the range of 150–180/85–95 mm Hg. Dietary compliance was determined by history only and was not rigorously controlled. Serum creatinine determinations, performed every 2 to 3 months, fluctuated between 5.0 and 5.9 mg/dl over the 3-year period of followup. The most recent findings are: serum creatinine, 6.4 mg/dl; creatinine clearance, 6.4 ml/min; BUN, 78 mg/dl; and urine protein excretion, 1 g/24 hrs. Protein intake, calculated from the 24-hour urea excretion rate plus an estimated excretion of non-urea nitrogen of 2.5 g/day, has been approximately 40 g/day. The patient continues to function normally and to feel well and has not developed any symptoms or signs that suggest uremia.

Discussion

DR. LEON G. FINE (*Chief, Division of Nephrology, Center for the Health Sciences, and Professor of Medicine, UCLA School of Medicine, Los Angeles, California*): We are currently in the midst of a flurry of investigational activity that has raised the hope that the downhill course of many human chronic renal diseases may be retarded or perhaps even arrested. Much of this optimism is based on the results of studies in experimental animals. While such studies clearly have advanced our understanding of the pathophysiologic mechanisms of nephron destruction, it is not at all clear that extrapolations safely can be made to human disease. Furthermore, even where such extrapolations appear to be appropriate based on our understanding of the physiology of the human kidney, there are quantitative considerations that might make the disease process in humans either more or less treatable than it is in the animal models.

My discussion will first compare animal models of experimental renal diseases with renal diseases in humans. Then I will consider the factors that contribute to the progressive nature of these diseases, emphasizing the applicability of proposed pathophysiologic processes to human disease. I will appraise current

Table 1. Long-term effects of reduction of renal mass on glomerular function in different species

Species	Model	Outcome	References
Rat	Uninephrectomy + contralateral subtotal nephrectomy	Progressive reduction of GFR	1, 2, 3, 15, 29, 32, 33
Rabbit	Uninephrectomy + contralateral subtotal nephrectomy	No reduction of GFR	8
Dog	Uninephrectomy + contralateral subtotal nephrectomy	No reduction of GFR	10, 16
Human	Uninephrectomy	No reduction of GFR	17, 18, 19

approaches to therapy and will evaluate the efficacy of these approaches in human renal failure. Finally, I will propose a hypothetical framework for an approach for predicting the patient's response to therapy.

Natural history of experimental and human renal disease

Subtotal renal ablation. Subtotal nephrectomy, including unilateral nephrectomy, leads to changes in the function of the remaining nephrons in rats [1–3], rabbits [4–8], dogs [9–10], and humans [11–13]. These changes include an immediate elevation in single-nephron glomerular filtration rate (that is, hyperfiltration), hypertrophy of all parts of the nephron, and adaptations in tubular reabsorptive and secretory processes. As early as 1932, Chanutin and Ferris observed that removal of three-quarters of the total renal mass in the rat led to a slowly progressive deterioration in the function of the remaining nephrons, with progressive azotemia and glomerular sclerosis [1]. This glomerular lesion of the remnant kidney is associated with significant proteinuria, which is now known to be due to loss of charge-selectivity and size-selectivity of the glomerular capillary wall [14]. Of interest is the fact that, in rats on a high-protein diet, even unilateral nephrectomy leads to significant proteinuria and glomerular sclerosis after 8 months, without a decline in GFR [15]. This observation is important, because reliable information in humans is confined to the effects of uninephrectomy, as I will discuss later.

Does this sclerotic glomerular lesion, which is so consistently observed in rats, also occur in other species, especially in humans? The literature suggests that it does not. Table 1 compares the long-term effects of reduction of renal mass in different species. Subtotal nephrectomy in the rabbit leads to a progressive interstitial fibrotic reaction in the remaining renal tissue [4, 8] but does not compromise glomerular structure over a 6-month period [8]. There are few long-term studies in dogs with remnant kidneys, but in two studies extending for 2 and 4 years respectively (a long time in the life of a dog!), the GFR did not deteriorate with time irrespective of the level of protein intake [10, 16]. Limited studies in humans likewise have failed to show that ablation of renal mass compromises the function of the remaining nephrons. Most of the evidence in this regard is obtained in long-term followup of donors of kidneys for transplantation. Although there appears to be a slightly increased incidence of mild proteinuria and mild hypertension in these individuals [17], followup periods of more than 10 years fail to reveal functional deterioration, even in the presence of hypertension [18]. Although the levels of proteinuria and blood pressure in these donors are usually compared to values in age-, sex-, and race-matched controls, the possibility must be considered that this population, being related to patients with renal disease and hypertension, might be genetically predisposed to hypertension with associated mild proteinuria, and that the higher incidence of these findings is unrelated to the loss of a kidney. The fact that the magnitude of proteinuria does not correlate with duration of followup [18] suggests that a progressive, acquired glomerular injury is not the cause of the proteinuria. What is needed for future studies is a comparably matched control group of siblings of transplant recipients who have not donated a kidney.

Robitaille et al recently reported on a long-term followup of 32 patients who had undergone unilateral nephrectomy in childhood (mean age 2.1 years) for tumor, dysplasia, hydronephrosis, or trauma [19]. No evidence for an increased incidence of impaired renal function or hypertension could be found after a mean followup period of 23 years when compared with 24 healthy control subjects of similar age.

Thus, no convincing evidence exists to indicate that progressive renal injury follows reduction of renal mass by 50% in humans, but whether progressive damage occurs in patients with greater degrees of renal ablation is not known. In anecdotal reports in which progressive disease appears to follow extensive renal ablation, it is important to exclude the role of untreated systemic hypertension (perhaps mediated by ischemia in the remnant kidney) as a causal factor. Although deterioration of renal function has been found with unilateral renal agenesis, bilateral cortical necrosis, and vesicoureteral reflux, all of which are associated with a reduction of the nephron population [20], the same damage that mediated the initial loss of function in these diseases might be responsible for the subsequent downhill course of the disease.

Glomerulopathies. The progressive nature of human glomerulonephritis and other glomerulopathies, particularly diabetic glomerulosclerosis, has spawned a number of experimental models that have been used to study mechanisms of progression.

In animal models of disease, the same hyperfiltration (that is, an increase in single-nephron glomerular filtration rate) that occurs in the remnant kidney occurs in rats with streptozotocin-induced diabetes mellitus [21]. In this model the glomerular lesion is progressive, associated with proteinuria, and aggravated by unilateral nephrectomy. In contrast, the BB rat strain with congenital diabetes mellitus also demonstrates an increase in GFR, but in this model renal function remains stable, and the rat does not develop proteinuria [22]. Experimental glomerulonephritis is accompanied by heterogeneous nephron injury [23] and a wide dispersion of values for single-nephron GFR (SNGFR) [24]. Some nephrons, however, presumably escape injury; in these, GFR increases and hypertrophy occurs. Ultimately, all the nephrons are destroyed, including those that initially appeared to be intact.

In a number of human renal diseases, an increase in GFR may occur during the earlier phases of the disease. In nonglomerular (tubulointerstitial) disease, a rise in SNGFR is the rule [25]. The early stages of human juvenile-onset diabetes are associated with a rise in GFR, which precedes the onset of microalbuminuria, overt proteinuria, and the ultimate fall in GFR; all these

attend nephron destruction [26–28]. Although direct measurements of GFR in individual nephrons obviously are not available in humans, the observation by Oliver that some glomeruli in human chronic glomerulonephritis are enlarged and are attached to hypertrophied tubules [23] suggests that some nephrons escape damage early in the process and undergo compensatory adaptations, which include a rise in SNGFR. Again, diffuse destruction of all nephrons characterizes the terminal stage of human glomerulonephritis.

Why is renal disease progressive?

Three postulates have been invoked to explain the progressive nature of renal disease. These are (*1*) ongoing injury due to the primary cause of the disease, (*2*) secondary injury to glomeruli, either due to compensatory adaptations in uninvolved or minimally involved glomeruli, or to intraglomerular coagulation abnormalities, and (*3*) secondary injury due to compensatory adaptations or alterations in tubular and interstitial function. In certain cases it is difficult to separate glomerular from tubular or interstitial abnormalities, but these three postulates will be considered separately for the sake of clarity.

Ongoing injury due to the primary cause of the renal disease

Unfortunately, the primary cause of the injury is understood in very few progressive, primary renal diseases. In addition, the offending cause can be eliminated in only a small number of disorders. Apart from infectious causes of immunologically mediated glomerulonephritis, one example of an "idiopathic" disease that can be arrested by removal of an identifiable cause of the insult is anti-glomerular basement membrane (GBM) disease. Although the primary cause of the rise in anti-GBM antibody is unknown, removal of the offending antibody by means of plasmapheresis may attenuate or prevent damage to the kidney. Other examples are the prevention of renal injury in many patients with essential hypertension by lowering the blood pressure, and the arrest of tubulointerstitial disease by removing an offending drug or toxin. Until the injurious agents that initiate a variety of primary glomerulonephritides are discovered, our efforts must be directed towards limiting secondary effects that aggravate the condition. This discussion, therefore, will not consider pharmacologic approaches to suppression of primary injury in the kidney.

Secondary injury due to glomerular capillary hypertension

The recent focus of attention on the "hyperfiltration" concept of secondary renal injury is due to the appealing simplicity of the concept and the impressive data from experimental studies by Brenner, Hostetter, Meyer, and colleagues over the past 5 years [15, 20, 29, 30–34]. The idea that adaptations in glomerular function could lead to progression of disease was first proposed in 1975 by Shimamura and Morrison, who stated: "The earlier clear demonstration of hyperfiltration in the glomeruli remaining after partial 5/6 nephrectomy appears to us as the most likely basis for the alteration in glomerular morphology observed. . . ." [2]. This concept suggests that the cause of progression of the glomerular lesion is the very compensatory increase in SNGFR of surviving glomeruli that, if viewed teleologically, alleviates the reduction in total GFR caused by the initiating injury [20]. In the rat remnant kidney [30], as well as in streptozotocin-induced diabetes mellitus [21], elevated glomerular plasma flow and elevated glomerular capillary hydraulic pressure (the latter will be referred to as "glomerular hypertension") have been observed. Because a high protein intake increases glomerular filtration rate [29, 35] and glomerular capillary pressure [29], and because reduction of protein intake in these experimental models blunts the hyperfiltration response and limits the extent of the glomerular injury and proteinuria [15], it has been suggested that some aspect of hyperfiltration causes progression of renal disease [29].

Table 2. Criteria required to establish that glomerular hypertension is a common pathogenetic factor in progressive glomerular injury

1. In all species in which it occurs, sustained glomerular hypertension should lead to progressive glomerular injury.
2. Prevention or early reversal of glomerular hypertension should prevent or arrest, respectively, progression of glomerular injury.
3. In heterogeneous forms of glomerular injury, a direct correlation should exist between maximum glomerular capillary pressure and the degree of sclerosis in the same glomerulus.

The hyperfiltration concept has been further refined by the demonstration that glomerular hypertension, not increased plasma flow, leads to renal injury [31]. This conclusion comes from observations in rats in which protein intake has been reduced only after the renal injury has become established; in this case, protein restriction does not affect the elevated glomerular plasma flow, but does reduce glomerular capillary hydraulic pressure [31]. These alterations are associated with reduced glomerular injury and macromolecule clearance as well as with preservation of GFR. An additional clue to the primacy of glomerular hypertension in the pathogenesis of progressive glomerular sclerosis is the observation that converting enzyme inhibitors protect the rat remnant kidney [32, 33] and the kidney of rats with streptozotocin-induced diabetes mellitus [34] against progressive glomerular damage. Reversal of the constrictive effects of angiotensin II on the efferent arteriole by these agents does not alter the elevated glomerular plasma flow and filtration rate, but it does reduce glomerular capillary hydraulic pressure. Recently a calcium-channel blocking agent, verapamil, also was shown to slow the progression of disease in the rat remnant kidney model [36]. Although calcium deposition might contribute to renal injury in this model [37], it is possible that this protection is due to a hemodynamic effect rather than to an effect on tissue calcium accumulation.

These observations have fueled the speculation that progressive renal damage in such disparate diseases as mineralocorticoid-salt hypertension, radiation nephritis, nephrotoxic serum nephritis, bilateral cortical necrosis, and unilateral renal agenesis is due to hyperfiltration injury [20]. Are such far-reaching speculations justified and, even if valid in the rat, how applicable are they to human glomerular disease? We can assess the strength of the evidence favoring the broad applicability of this concept by applying some simple "Koch-type" postulates to the available data (as shown in Table 2). If the progression of renal disease is due to glomerular hypertension, the following would be expected: (*1*) In previously intact nephrons as well as in diseased nephrons, glomerular hypertension—if sustained for a sufficient period of time by any maneuver—should produce progressive loss of glomerular function. (*2*) Reversal of glomer-

ular hypertension should slow or arrest progression of glomerular disease. (*3*) A direct correlation should exist between the glomerular capillary pressure and the extent of glomerular sclerosis in the same glomerulus [38].

I will now turn to an analysis of the evidence indicating that there are sufficient deviations from these postulates to raise doubt about the pathogenetic role of glomerular hypertension in progressive glomerular sclerosis. I should point out first that some of the most recent information cited here is available in preliminary (abstract) form only and awaits definitive confirmation.

Inconsistent relationship between hyperfiltration and glomerular sclerosis in experimental renal disease. As I pointed out, a compensatory increase in GFR follows renal ablation in the human, dog, rabbit, and rat. This increase has been documented in single nephrons in dog and rat in micropuncture studies. Because of the unique location of glomeruli on the surface of the Munich-Wistar rat kidney, glomerular capillary pressure has been measured directly only in this species. We can reasonably assume that the factors that mediate the elevation of SNGFR in this species would lead to a rise in SNGFR in all species. Why, then, does glomerular sclerosis only occur in the rat?

One possibility is that the relationship between glomerular hypertension and sclerosis is neither causal nor consistent. Yoshida et al recently reported in abstract that, when glomerular capillary pressure is measured repeatedly in the same glomeruli of the rat remnant kidney over a 6-week period, so that functional and structural changes can be monitored longitudinally in each, the variations in SNGFR and capillary pressures among glomeruli are not well correlated [38]. Whereas the degree of glomerular sclerosis is greatest in the glomeruli with the lowest GFRs, no correlation exists between the ultimate level of SNGFR and the maximum glomerular capillary pressure recorded in the earlier stage of the disease. These studies suggest that glomerular hypertension is not necessarily the forerunner of subsequent functional and structural damage.

Further, Purkerson and colleagues were able to reduce the severity of progressive renal disease in rats with subtotal renal ablation by using an inhibitor of thromboxane synthesis [39]. This protection occurred despite a near doubling of the GFR and renal plasma flow rate, that is, despite marked hyperfiltration. Unfortunately, glomerular capillary pressure was not measured in these experiments, and systemic blood pressure was lower in the rats treated with the thromboxane inhibitor. It is therefore possible that, if equivalent dilation of afferent and efferent arterioles was achieved, a rise in plasma flow and GFR could have occurred in the absence of a rise in glomerular capillary pressure, especially if blood pressure was lowered.

Observations in experimental glomerular disease also argue against the notion of a fixed relationship between hyperfiltration and glomerular injury. In streptozotocin-induced diabetes mellitus, reversal of glomerular hypertension with a converting enzyme inhibitor reduces proteinuria and the tendency of the glomerulus to undergo sclerosis [34]. However, Bank and colleagues, studying streptozotocin-induced diabetes in normotensive (WKY) and hypertensive (SHR) rats, showed that glomerular capillary pressure (P_{GC}) is exaggerated in the SHR rats within 7 days but that no differences in glomerular morphology between normotensive and hypertensive animals were evident after 6 months, despite the fact that the elevated P_{GC} was sustained for this period [40]. In these studies, the normotensive WKY diabetic rats had higher levels of P_{GC} than did their nondiabetic littermates and it could be argued that this glomerular hypertension was sufficient to initiate the observed mesangial expansion and proteinuria in this group. This, however, does not appear to be the case, because diabetic SHR rats maintained normotensive with drugs had the same elevated P_{GC} as did diabetic WKY rats and yet had significantly less mesangial expansion and proteinuria. These data thus fail to support a causal relationship between glomerular capillary hypertension and glomerular injury in this model. In the BB strain of rat with congenital diabetes mellitus, GFR also increases early in life above the levels observed in nondiabetic littermates, but with no tendency toward the development of renal disease [22]. It is not known whether glomerular hypertension occurs in this model.

In doxorubicin- and puromycin-aminonucleoside-induced renal injury in the rat, glomerular capillary pressure does not appear to correlate with evolution of proteinuria or focal glomerulosclerosis. Fogo and coworkers performed serial micropuncture measurements in the same glomeruli in both of these disease models, and in preliminary studies found no correlation between glomerular capillary pressure and glomerular sclerosis [41]. Nevertheless, SNGFR declined progressively due to focal glomerulosclerosis. Treatment with captopril attenuated the degree of sclerosis without affecting SNGFR or glomerular capillary pressure in the earlier stages. In short, the development of glomerular sclerosis might not be related to the occurrence of glomerular hypertension in a number of experimental models of glomerular disease, even in the rat.

Lack of evidence that hyperfiltration leads to progressive renal failure in humans. As I already mentioned, uninephrectomy in renal transplant donors leads to hyperfiltration without notable adverse effects in humans. In normal individuals, an amino acid infusion [42] or a meat meal [35, 43] can induce acute glomerular hyperfiltration. Chronic intravenous administration of amino acids in patients receiving total parenteral nutrition leads to nephromegaly [44]; renal size increases progressively as long as the parenteral nutrition is continued and decreases when the infusion is discontinued. Abundant evidence shows that renal size and GFR are positively correlated in this setting [25] and we can assume that the GFR in such individuals remains persistently elevated for the duration of the parenteral nutrition. I am unaware of any reports of renal damage during prolonged total parenteral nutrition. Taken together, these considerations cast doubt on the causal relationship between glomerular hypertension and progression of renal disease in humans.

Secondary injury due to alterations in tubular and interstitial function

The knowledge that calcium deposits commonly occur in the interstitium of chronically diseased kidneys [45] led to a series of rat studies that attempted to unravel the pathophysiologic events leading to such deposition. The degree of calcification and fibrosis appears to be closely correlated with serum phosphorus levels, and calcium-phosphate deposition occurred presumably as a consequence of a rise in the calcium-phosphorus

product [46]. The logical preventive measure therefore was restriction of dietary phosphorus intake. This maneuver proved beneficial both in the rat remnant kidney [47] and in nephrotoxic serum nephritis models [48]. Not only was proteinuria reduced in both models, but so was mortality from renal failure.

Because renal calcification is a well-recognized complication of the secondary hyperparathyroidism of uremia, the effect of removal of the parathyroid glands was evaluated. Thyroparathyroidectomy proved effective in reducing the progression of nephrotoxic serum nephritis, but selective parathyroidectomy, surprisingly, was without effect [49]. The inevitable conclusion that thyroid hormone is somehow linked to progression of renal disease remained without further explanation for a number of years. Recently, however, Conger and Falk reported preliminary data in the remnant kidney model which indicate that thyroidectomy reduces SNGFR, glomerular capillary pressure, and urinary protein excretion [50]. Replacement with thyroid hormone or isoproterenol restored these parameters to prethyroidectomy levels. In view of the known tendency of hypothyroidism to attenuate the hypertrophic response of the kidney, and the ability of isoproterenol to reverse the effects of thyroidectomy on GFR [50], thyroid hormone deficiency probably reduces the likelihood that experimental renal disease will progress. Unfortunately, these results do not elucidate the mechanism of the protective effects of phosphate restriction.

Assessing the protective effect of phosphate restriction is difficult because experimental phosphate restriction often is accompanied by dietary protein restriction. Lumlertgul and coworkers achieved isolated phosphate restriction in rats with remnant kidneys by administering the phosphate binder dihydroxy-aluminum aminoacetate [51]. This approach produced no change in protein intake or weight loss but nevertheless was highly effective in reducing proteinuria and preventing the long-term fall in GFR that occurs in these animals when they are fed a phosphate-rich diet. Although the role of phosphate is discussed here in the context of tubulointerstitial injury, it is theoretically possible that the protective effects of phosphate restriction are mediated by primary effects on glomerular function.

Nath et al have proposed an innovative explanation for the progressive interstitial fibrosis that consistently appears in the remnant kidney. Feeding rats bicarbonate reduced this fibrosis [52]. The authors noted that bicarbonate-fed rats had fewer deposits of C3 and C5b-9 than did sodium chloride-fed rats. These authors proposed that the dietary alkaline load reduced tubular ammonia production. Because nitrogen nucleophiles, such as ammonia, react with complement component C3 to form a convertase for the alternative complement pathway, reduction of tissue levels of ammonia by bicarbonate was thought to reduce tissue damage by this mechanism.

Efficacy of therapy in human renal disease

Control of systemic blood pressure

Much emphasis has been placed on the observation that, in any given patient, regardless of the nature of the disease process, the reciprocal of the serum creatinine concentration (1/[Cr]) is a linear function of time and that a change in the slope of this relationship reflects a change in the intrinsic rate of progression [53]. The argument holds that if a linear decline in 1/[Cr] is valid for all patients with all renal diseases, then patients can serve as their own controls, and the need for comparing different patient groups is obviated.

How infallible is this argument? Can the slope of the 1/[Cr] relationship be altered by factors other than any single therapeutic modality under study? This issue has been raised by El Nahas and Coles [54], who cogently point out that failure to take into account spontaneous stabilization of renal function, changes in muscle mass, alterations in creatinine intake, extent of proteinuria and, importantly, the apparently beneficial effect of frequent followup visits and blood pressure control might account for some of the apparently beneficial results of protein restriction and other manipulations. One example of the beneficial impact of blood pressure control and close followup is highlighted by two reports from the same laboratory. In 1983 Alvestrand and colleagues reported the beneficial effects of a new amino acid preparation administered for an average period of 224 days to 15 uremic patients [55]. In 4 patients in whom progression of disease was assessed by the slope of 1/[Cr], renal disease dramatically slowed or stopped. In these patients the serum creatinine data were compared retrospectively with prospective data gathered from the inception of the dietary intervention. Three years later, the same group reported on 17 patients with chronic renal failure (creatinine clearance 12–66 ml/min) who were entered into a study that entailed no specific dietary change but that required frequent followup and acceptable blood pressure control [56]. (Of course, unintentional changes in patients' dietary habits after enrollment that were not directed by the study cannot be excluded.) The rate of progression of renal failure slowed significantly after the patients entered the study. This important observation raises the possibility that improvement in renal function that earlier had been attributed to dietary manipulations might have had some other cause.

It is accepted dogma that control of blood pressure limits renal injury in essential hypertension and in experimental models of hypertension. But careful documentation of the effects of blood pressure control on progression of human renal disease is limited. The role of blood pressure as a determinant of the development of diabetic nephropathy recently has come under scrutiny. Parving and coworkers found that diabetic patients with proteinuria had higher blood pressures than did diabetic patients without proteinuria when the groups were matched for gender, age, body weight, and duration of diabetes [57]. Similar findings were reported from the Joslin Clinic, where hypertension was found in 81% of juvenile-onset diabetics with microalbuminuria but in only 32% of matched controls without it [58]. A genetic predisposition to hypertension was proposed as a major determinant of diabetic nephropathy [58]. Early, aggressive antihypertensive treatment for approximately 3 years has been shown to reduce the rate of decline of GFR in the absence of a change in metabolic control of diabetes [59]. Baldwin and Neugarten summarized the evidence that control of hypertension is beneficial in experimental models of glomerular disease, in human glomerulonephritis, and in diabetic nephropathy [60]. Overwhelming evidence indicates that hypertension aggravates glomerular injury in all circumstances and that altered glomerular hemodynamics in disease magnifies the transmission of the high systemic blood pressure to the glomerulus, leading to an accelerated rate of injury [60]. Control of

systemic hypertension thus plays a critical role in limiting hemodynamic stress on the glomerulus [60].

Reduction of hemodynamically mediated glomerular injury

In the following section, I will analyze clinical studies designed to retard the progression of renal disease, ostensibly by reducing or reversing glomerular hypertension.

Dietary protein restriction. The effects of protein restriction in azotemic humans are difficult to evaluate in view of the uncontrolled nature of most of the published studies. In 1975, Johnson et al restricted protein intake and reduced phosphorus absorption in patients with renal failure. The rise in serum creatinine over the subsequent 2 years was slower than that observed in untreated patients, but no controls were available to determine the effect of close followup and blood pressure control [61]. In 1982, Maschio and colleagues described the effects of dietary protein and phosphorus restriction in 75 patients with renal failure followed for 18 to 76 months [62]. The slope of 1/[Cr] in patients with moderate (mean serum creatinine concentration, 2.18 mg/dl) and severe (mean serum creatinine, 4.2 mg/dl) renal failure was reduced. These patients were compared with a group of patients with a mean serum creatinine of 2.28 mg/dl who were ingesting an unrestricted diet. Fully 50% to 80% of the patients were described as being hypertensive, however, and no documentation is given as to the efficacy of blood pressure control in the different groups. It is also not clear whether the patients whose diets were restricted were monitored more frequently than were untreated patients. A subsequent study by the same group examined the effects of a low-protein diet in patients with chronic glomerulonephritis, polycystic kidney disease, or chronic pyelonephritis [63]. The untreated control group was studied retrospectively; thus it is difficult to evaluate the claim that deterioration of renal function was slowed.

El Nahas and coworkers also subdivided their patients according to the nature of the underlying disease and were able to demonstrate slowing of functional deterioration in the presence of a low-protein diet only in the group with tubulointerstitial disease [64]. This prospective study appears to have been well controlled, with patients being followed for 6 months while eating a normal-protein diet, and then for an additional 6 months eating a low-protein diet. No effect was seen in patients with polycystic disease or hypertensive nephrosclerosis, and only a marginal response was obtained in those with chronic glomerulonephritis.

Low-protein diets have been supplemented with various essential amino acids and keto-analogues of essential amino acids in an attempt to maintain nitrogen balance [65]. Despite the ability of these diets to maintain positive nitrogen balance, their value in arresting the progress of renal disease requires further study. The studies by Alvestrand et al that I cited suffer from the drawback that prospective and retrospective data are compared [55]. Attman and colleagues found that residual renal function continued to deteriorate over a mean followup period of 5 months in a group of patients with diabetes and severe renal failure (GFR in the range of 7.5 ml/min) who were treated with a diet of 20 to 30 g/day of protein supplemented with essential amino acids [65]. After 12 months, only 2 of 21 patients had not developed progressive renal failure requiring dialysis or transplantation.

Mitch et al treated 24 patients who had chronic renal failure with a low-phosphorus diet containing 20 to 30 g of protein supplemented with amino acids and their keto-analogues [66]. The decline in renal function slowed in 10 of 17 patients. Six of these patients had a serum creatinine value of 8 mg/dl or higher at the time of entry; that value showed no tendency to decline over an average of 22 months. Again, the effects of better blood pressure control during the prospective phase of the study and the proportion of patients with spontaneous stabilization of function cannot be determined. Although the authors contended that "there is no evidence that progression of chronic renal failure is slowed by more frequent visits," this conclusion is open to question. A comparison of an average prospective followup period of 20 months, with an average retrospective evaluation period of 32 months, masks the fact that the frequency of visits appears to have been much greater in the prospective phase [66].

The only prospective, randomized trial reported thus far was performed by Rosman et al, who followed 149 patients for at least 18 months. The average rate of fall of 1/[Cr] was significantly slower in patients maintained on a diet of 0.4–0.6/kg body weight of protein daily than in control patients who continued their usual diet [67]. Control of blood pressure and serum calcium and phosphorus was the same for all patients. Blood pressure control was obtained with diuretics, beta blockers, and vasodilators such as prazosin and hydralazine. The protective effect of the low-protein diet was equally evident in patients entering the study with GFRs less than 30 ml/min/1.73 m^2 and in patients with GFRs greater than 30 ml/min/1.73 m^2. Preliminary data reported by Zeller and colleagues appear to confirm the beneficial effects of dietary protein restriction in diabetic nephropathy over 10 to 15 months in a randomized, prospective study in which blood pressure was well controlled [68].

Pharmacologic manipulation of glomerular capillary pressure. The observation that converting enzyme inhibitors impede the progression of renal disease in rat models has raised the possibility that such therapy might have a place in human disease. Unfortunately little information is available in humans. Taguma et al reported that captopril reduced proteinuria in patients with advanced diabetic nephropathy [69], but the duration of the study was too short to evaluate an effect on GFR. A more recent report in insulin-dependent diabetics with nephropathy showed that 12 weeks of captopril therapy reduced proteinuria but also caused a small but significant reduction in GFR [70]. Although a reduction of GFR is not deleterious at this level of renal function and may, indeed, turn out to be protective, it clearly indicates that converting enzyme inhibitors might have to be used with caution in diabetic patients with advanced renal failure for fear of "tipping the scales" in a previously stable patient, and thereby causing uremia.

Some investigators have inferred from the rat remnant kidney model that converting enzyme inhibitors are more effective than are other antihypertensive drugs in preventing progression of renal disease [32–34]. In human disease, the validity of this assertion needs to be established. As I discussed previously, control of hypertension by conventional means does appear to slow the progress of renal failure. But a theoretical problem that could arise with the overly enthusiastic use of converting enzyme inhibitors in advanced renal disease is that GFR could fall in situations in which ultrafiltration strongly depends on

efferent arteriolar tone. In moderate to severe renal failure in hypertensive patients, this concern probably is not warranted, because the current evidence suggests that GFR is well maintained [71]. It is not clear whether this finding applies to patients with diabetic nephropathy.

If systemic hypertension is central to the progression of human disease, antihypertensive agents are required that can maintain renal plasma flow and GFR despite a reduction of systemic blood pressure. Candidates for this role are the dopamine agonists and the calcium channel-blocking agents. Ibopamine, a dopamine-like agent, was effective in slowing deterioration of, or even improving, renal function in patients with nonglomerular renal diseases over a 6-month period [72]. Unfortunately, these studies also compared retrospective and prospective data and, other than serum creatinine measurements, no other renal functional parameters were provided. Goldberg has suggested that, because a decrease in renal perfusion is common in hypertensive states, and because hypertension either causes, or is associated with, chronic renal disease, activation of dopamine receptors might be useful in preventing impairment of renal function. Dopamine itself is unsuitable because of its poor bioavailability and alpha-adrenoceptor vasoconstrictor actions [73]. Potential candidates would be oral agents that have effects mainly on dopamine 1 (DA1) receptors, which predominate in the kidney. Such agents would include levodopa and fenoldopam, which increase renal blood flow while lowering blood pressure. The effects of calcium channel blockers on renal hemodynamics are not well studied in humans, but thus far these agents do not seem to depress GFR in patients with compromised renal function [74].

Dietary phosphorus restriction. As I pointed out, it is difficult to separate the selective effects of protein restriction and phosphorus restriction in low-protein diets; most early studies combined restriction of both. Nevertheless, data in the literature do address the role of phosphorus intake in the rate of progression of renal failure. Barsotti and coworkers reported on 2 comparable groups of patients with early chronic renal failure [75]. Followed prospectively, these patients had the same protein and caloric intake but different phosphorus intakes (6.6 versus 12.0 mg/kg/day). When the patients were switched from their free diets to the controlled diets, creatinine clearances were similar (20 ml/min) and the rate of fall in creatinine clearance slowed in both groups. Although a slower rate of decline of renal function was observed in patients eating the low-phosphorus diet, the final mean creatinine clearances differed only by 4 ml/min at the end of 16 to 20 months. These results are similar to those reported earlier by Barrientos et al, who failed to find a protective effect of dietary phosphate restriction on progression of renal disease [76].

Anticoagulant therapy. The role of microvascular coagulation abnormalities in the progression of renal disease has been suggested by anecdotal reports, but few controlled data are available. The one controlled situation is in patients with membranoproliferative glomerulonephritis. Donadio reported that platelet inhibitor therapy with dipyridamole and aspirin resulted in fewer cases of end-stage renal disease (3 of 21 patients after 62 months) when compared with a control group (9 of 19 patients after 33 months) [77]. Zimmerman et al conducted a similar prospective study using warfarin and dipyridamole and showed stabilization of renal function in the treated groups, but not in the control group [78]. When patients were "crossed-over" (treatment to control and vice-versa), significant changes in renal function were observed.

The concept of "glomerular tolerance"

Over the past few years, heavy emphasis has been placed on the results of studies of animal models of renal disease. These results point the way to new approaches for slowing the progression of human renal disease. Important pathophysiologic principles have emanated from such studies, but important pitfalls also have emerged. In many cases, the models are sufficiently different from human disease—either quantitatively or qualitatively—as to be of questionable relevance. Differences in the natural history of the same disease model from species to species (such as the remnant kidney) highlight the difficulty of simple extrapolation. Therapeutic maneuvers that reduce glomerular hypertension are effective in slowing progression or reducing proteinuria in some animal models but not in others. Finally, the evidence in support of the causal relationship between glomerular hypertension and progression of renal disease in humans is tenuous.

In considering the results of these studies, I should like to propose a hypothesis that could explain many, if not all, the discrepant results. I have called this hypothesis "glomerular tolerance." If, in a previously intact rat glomerulus, hemodynamic alterations are responsible for eventual proteinuria and glomerular sclerosis, shouldn't these changes apply to all species affected by a comparable degree of hyperfiltration? Perhaps it is not the degree of hyperfiltration that causes injury, but also the "tolerance" of the glomerulus to the hemodynamic stress. That is, maybe quantitative differences in the threshold for injury exist between intact and diseased nephrons in the same species and between intact nephrons of different species.

This argument is supported by two sets of observations: (*1*) The elevation in GFR following renal ablation is probably similar in all species [25], as shown by micropuncture studies of SNGFR in rats [30] and dogs [79] with remnant kidneys and by the fact that, at minimum, a doubling of SNGFR must occur in humans to restore serum creatinine concentration to normal following unilateral nephrectomy [18]. (*2*) The rise in GFR that follows a meat meal in humans, an increase that is termed "renal reserve," is the same in normal kidneys as in diseased kidneys [80]. Although initial studies suggested decreased "renal reserve" in response to a meat meal in patients with renal disease [43], recent studies show an intact "reserve" in such patients [80, 81]. It is therefore unlikely that the magnitude of the hyperfiltration is the variable that accounts for progression of disease in one situation but not another.

The hypothetical concept of "glomerular tolerance" is illustrated in Figure 1, in which rats and humans are depicted as having the same absolute level of SNGFR. The absolute rise in GFR following renal ablation is similar in both. However, the propensity for injury following renal ablation depends on the relationship between the elevated GFR and some hypothetical injury threshold. The analogy could be equally applied to the streptozotocin-induced versus the BB diabetic rat; the injury threshold may simply be higher in the latter. This hypothesis proposes that it is not "renal reserve" that predicts the tendency toward progression of disease, but some other parameter(s) reflecting susceptibility to injury. One explanation for

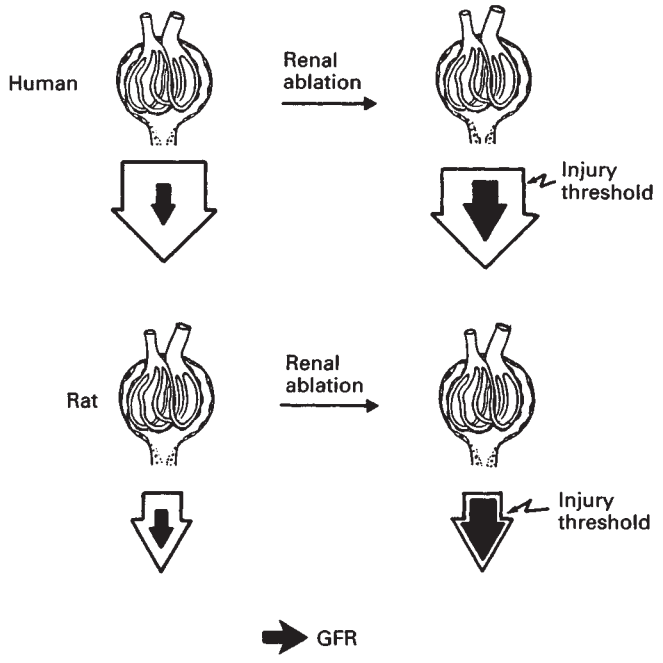

Fig. 1. *The concept of glomerular tolerance as illustrated by a comparison of the response of the glomerulus in the human and the rat to renal ablation.* The basal GFR and the increase in GFR following renal ablation are similar (*dark arrows*). The hypothetical difference between the two species is that the injury threshold (*open arrows*) is greater in humans than in rats. Thus, the hemodynamic adaptation approaches the injury threshold more readily in rats than in humans, making the glomerulus of the former more susceptible to injury.

such a variable susceptibility could be differences in the autoregulatory capacity of the glomerulus, such that systemic blood pressure is transmitted more effectively to the glomerular capillaries in certain species or disease states than in others [82, 83]. This variation might be due to differences in the production of, or sensitivity to, vasoactive substances within the kidney or to intrinsic structural constraints.

Concerning clinical trials designed to retard the progression of renal disease, a study that separates the effects of selective reduction of glomerular hypertension and the effects of reduction of systemic hypertension in humans has not been carried out. To date, it appears that control of blood pressure is of central importance in this regard. There also appears to be a protective effect of low-protein diets, but the paucity of adequately controlled, prospective studies in patients leaves the value of this approach unproved. Furthermore, it is not clear whether dietary changes affect different disease states differently for any given level of renal function. Finally, there is no convincing evidence that selective reduction of phosphorus intake or absorption alters the course of human renal disease despite the evidence for such an effect in animals.

Let us return to my hypothetical concept of "glomerular tolerance." If glomerular tolerance could be measured in humans, it might be used as a predictor of progression of renal disease. I wish to propose a method for making such measurements. Two tests might be assessed: the response of proteinuria to colloid-induced volume expansion and the response to diuretic-induced volume contraction. One possible method would be to measure glomerular permselectivity to macromolecules (that is, proteinuria) in response to acute hyperfiltration. The fact that normal rats develop proteinuria in response to an acute protein load [84] and humans do not [80] suggests that changes in proteinuria might be a useful reflection of glomerular tolerance to hyperfiltration. For example, if uninephrectomy or intrinsic disease leads to subtle glomerular injury that does not cause overt signs of disease in the remaining nephrons, it might be possible to expose the silent initial damage by the superimposed stress of acute hyperfiltration. This maneuver, if it induced proteinuria, might thereby identify patients with lowered injury thresholds, that is, those more susceptible to the effects of long-term glomerular hypertension. Because urinary protein excretion does not seem to increase after an acute oral protein load in humans, even when biopsy-proved glomerular disease is present [80], a more reasonable approach might be to evaluate the effects of acute colloid volume expansion, which increases both albumin and IgG excretion in nephrotic patients but not in normal subjects [85]. This maneuver perhaps could identify a subgroup of patients with reduced glomerular tolerance.

A critical question remains: Are there, indeed, subpopulations of patients with decreased glomerular tolerance who show no manifestations of overt disease under baseline conditions, but who manifest proteinuria following an acute stress such as uninephrectomy? If such subpopulations could be defined, we could reasonably predict which patients are more likely to develop overt disease at a later stage, and we could thus institute preventive therapy selectively and appropriately. Furthermore, if maneuvers such as acute diuretic-induced volume contraction or low-protein intake [86] lead to decreased protein excretion in a subpopulation of patients with established glomerular disease, it would be reasonable to predict that these patients would benefit from a reduction of hemodynamic stress. The use of hyperoncotic albumin infusion as a proteinuric stimulus or the use of acute volume contraction to reduce proteinuria in patients with established glomerulopathies might prove useful methods of selecting patients who would benefit from a reduction in hemodynamic stress to the glomerulus. If an adaptation in glomerular function is beneficial and does not approach the injury threshold, the adaptation should be supported. On the other hand, if the adaptation exceeds this threshold, it should be prevented or reversed so as to preserve function. Currently there is no method for detecting and quantitating such a hypothetical threshold for injury.

An encouraging start has been made in understanding the factors that cause progression of human renal diseases. The time has come for us to apply more quantitative approaches to human studies, not only for assessing outcome but for predicting the response to therapy. This will enable physicians to select patients for different forms of treatment and thus to optimize the results of therapy.

Questions and answers

DR. JEROME P. KASSIRER (*Associate Physician-in-Chief, Department of Medicine, New England Medical Center, Boston, Massachusetts*): Perhaps you can clarify your concept of "glomerular tolerance." You propose to use hyperoncotic albumin and diuretics to assess this function. I assume you are propos-

ing that such tests be assessed, not that they be used clinically. Is that correct?

DR. FINE: Absolutely correct. I did not want to come here simply having analyzed the data in order to draw limited conclusions. I thought that if one could look at the data in experimental animals and then ask some questions pertinent to human disease, it might be possible to put the whole therapeutic approach into some sort of unifying conceptual framework. This is why I'm suggesting the term "glomerular tolerance." One looks at the relationship between the stress and the tolerance of the nephrons to that stress rather than just looking at the stress, as everybody has done up to now. But you are entirely correct; the last part of what I talked about is simply a series of suggestions about how we might start thinking about this.

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center*): Dr. Fine, you pointed out that various species exhibit hyperfiltration following partial renal ablation, but that only the rat develops glomerulosclerosis. What do you think is the basis for that? Do you imply that for the same change in GFR, the glomerular capillary pressure is different among the various species? Is it possible that the difference reflects, at least in part, variable degrees of renal ablation and differences in the time frame over which observations are made? Finally, referring to your concept of "glomerular tolerance," what is the evidence that the hemodynamic stress to the glomerulus is similar across species?

DR. FINE: That is a key question and an unanswerable one because, even in the rat, glomerular capillary pressure can be measured directly only in the Munich-Wistar strain. In other strains, glomerular capillary pressure can be measured indirectly from stopped flow pressure. Unfortunately no pertinent data exist in rabbit or dog models. All I can tell you is that hyperfiltration does occur in all species. It occurs in humans and in the rabbit, as evidenced by total GFR measurements; in the rat and the dog it has been documented at the single nephron level. I suppose that it is theoretically possible that in the rabbit, in the dog, and in humans hyperfiltration occurs by virtue of a rise in plasma flow without glomerular hypertension and that this could be an alternative explanation as to why these species do not develop glomerulosclerosis. I would be surprised if this is the case. In fact, Brian Myers' group, who measured changes in derived glomerular capillary pressure (but not absolute values) in humans, showed that an acute meat meal elevates P_{GC} when GFR rises [80]. Thus, given the fact that the problem only occurs in one of four species, it is very difficult to apply principles derived from that species across species barriers because they simply might not be applicable. The one explanation I have focused on is an alteration in the injury threshold. You have stressed something that, perhaps, I should have emphasized, that is, that the magnitude of the stress can differ from species to species.

DR. JOHN T. HARRINGTON (*Chief of Medicine, Newton-Wellesley Hospital, Newton, Massachusetts*): In your analysis you seemed particularly impressed by the efficacy of blood pressure control in ameliorating the progression of chronic renal disease. Do you think that the mechanism involved is simply a reduction in glomerular hydraulic pressure, or does one have to invoke an additional mechanism?

DR. FINE: Basically, the mechanism is probably a reduction of transmitted pressure, but I refer you to a very good review on this topic by Baldwin and Neugarten [60]. It does appear as if higher systemic blood pressures are transmitted to the glomerulus. Thus, in humans at least, whatever method you use for reducing pressure does seem to have a protective effect.

DR. KASSIRER: Do we know anything more about the mechanisms by which changes in protein or amino acid intake change the GFR?

DR. FINE: The current investigative enthusiasm suggests that many people have tried to answer that question by identifying one or more humoral factors released in response to the protein or amino acid. Changes in GFR could, of course, be a direct effect on the glomerulus of raising the concentration of one or more amino acids. This seems less likely than the possibility that the dietary manipulation alters the level of one or more systemic or local hormones. The candidate hormones include growth hormone, glucagon, atrial natriuretic factor, and some of the vasodilator prostaglandins. Thus far no one has identified a single hormone, and because of what we know about what controls glomerular circulation, the mechanism is unlikely to be a single substance.

DR. PAUL S. KURTIN (*Chief, Division of Pediatric Nephrology, New England Medical Center*): What role, if any, do you think continuing growth of the organism plays? For example, the rats used in most studies are young rats that are growing throughout the study, whereas adult kidney donors are no longer growing. The difference might be important in light of a report of 8 children with unilateral renal agenesis who developed focal and segmental glomerulosclerosis in the remaining kidney [87].

DR. FINE: Dogma says that older patients do not undergo, or do not demonstrate, renal hypertrophy to the same extent as do younger patients. You are also suggesting that because hypertrophy seems to be closely linked to GFR and because humans don't show the sclerotic response, maybe the GFRs are not elevated. I have shown representative data indicating that human donors do, in fact, have elevated GFRs even though they are an older, mature population [18]. Their kidneys still undergo hypertrophy and hyperfiltration, so I don't think that the answer lies in the age at all. In fact, most renal donors are in the age group in whom satisfactory and complete hypertrophy and hyperfiltration do occur.

DR. KURTIN: But would you comment on McCluskey's data?

DR. FINE: The question with those data, whether they pertain to unilateral renal agenesis or reflux nephropathy, is: how do you confidently separate primary injury from secondary injury? The primary disease is a compounding factor and can affect the remaining kidney the same way it induced the initial injury. It may be true that the hemodynamic stress accentuates disease, but I think that it's very difficult to sort out when you've got some primary, underlying renal injury to contend with.

DR. RONALD D. PERRONE (*Division of Nephrology, New England Medical Center*): I think one of the problems with the Rosman study, which purported to show the benefit of protein restriction, is that the patients with low creatinine clearance who were assigned to a low-protein diet had a reduction in creatinine excretion towards the end of the study [67]. Rosman et al did not measure arm circumference, so it is unclear whether there was loss of muscle mass.

DR. FINE: In fact, the study you cite measured survival curves. You probably cannot do better than that.

DR. PERRONE: I would take it one step further. Although Mitch and coworkers have advocated the use of the reciprocal of serum creatinine [66], they previously reported that extrarenal creatinine metabolism takes on a significant role in patients with advanced renal failure [88]. It is possible that extrarenal creatinine degradation is an additional mechanism for stabilization of the serum creatinine in those patients.

DR. FINE: Yes, it is possible. One is forced to conclude that such studies should be conducted not only prospectively but with a more rigorous marker of GFR than the serum creatinine concentration.

DR. MADIAS: You referred to a difference between the BB diabetic rat and the rat with streptozotocin-induced diabetes in terms of development of advanced renal dysfunction, and you implied that renal disease might be an idiotypic feature of treatment with streptozotocin. What about other models of diabetes mellitus, for example, those induced by alloxan or pancreatectomy? Do they get renal damage?

DR. FINE: Since renal hypertrophy does occur in alloxan-induced diabetes [89], I assume that GFR also rises. I have no idea whether renal damage has been described in this model. Certainly streptozotocin is the most widely used experimental agent.

DR. KASSIRER: Let me offer a thought about the protein-restriction studies. Perhaps protein restriction is not highly efficacious, but because patients are now being followed much more closely and carefully, and blood pressure is being brought under control better (particularly with the effective drugs now available), renal function is better preserved now than it was before.

DR. FINE: I think that is partially true. We probably will find that in all ongoing studies the control groups will do considerably better than anybody has anticipated because of the close control of blood pressure. I think that your pessimism (and I hope that's too strong a word) about the effect of the protein diet might not be correct; there might be, and probably will be, an additional effect of a low-protein diet when all the data come in. But you're right about the control groups. In talking to colleagues, it is evident to me that this is now the general experience in treating patients with renal disease. Our patients seem to be doing much better than we would have anticipated at first visit, when they arrive with a serum creatinine concentration of 5 or 6 mg/dl. The patient presented today represents an example of this. Thus close followup needs to be stressed.

DR. HARRINGTON: Dr. Fine, you mentioned in passing the data of Alfrey regarding the rat subjected to thyroparathyroidectomy. The effects demonstrated were related to the presence or absence of the thyroid gland, not the parathyroid gland. Perhaps you could expand on that fascinating observation. Should we make all our patients hypothyroid!?

DR. FINE: Certainly not! Other than the observation that if a uninephrectomy is performed in a hypothyroid animal there is less tendency for the remaining kidney to hypertrophy [90], the simple explanation is that there is less tendency for the GFR to increase in hypothyroidism. Preliminary data suggest that the GFR decreases in a hypothyroid animal [50]. Thus the protective effect of thyroparathyroidectomy also might be mediated through a hemodynamic mechanism. If the hypothroid animal is given isoproterenol to restore the cardiac output and restore GFR, the selective effects of thyroid hormone deficiency can be studied independently of the hemodynamic effects. The results of such studies would be interesting, but my guess is that a hemodynamic event is playing a role in the protection afforded by thyroidectomy. I also remind you that these preliminary studies were performed in rats.

DR. PERRONE: I am intrigued by the protective effect of hypothyroidism. As we know, thyroid hormone stimulates sodium-potassium ATPase. Have there been any studies on the metabolic effects of low-protein diets or other protective maneuvers? Might not hemodynamic effects on metabolism, for example, be part of the protective effect?

DR. FINE: That is possible. I don't know of any studies that address your question directly. I think it is appropriate that these suggestions be raised; we clearly need to think about this problem as broadly as possible.

DR. HARRINGTON: Is there any evidence that the degree of reduction of blood pressure has a progressively protective effect? If you lower blood pressure to the upper level of normal, to normal, or to slightly below normal, do you obtain a differential effect on preservation of renal function?

DR. FINE: I don't know of any data measuring that. Clearly it would be a very difficult study. As we all know, when we ask our patients to measure their blood pressures at home and to write down the results, we are presented with numbers that often bear very little relationship to those we obtain from blood pressure measurements in the office. Perhaps the 24-hour monitoring approach will provide us with better data to evaluate this possibility.

DR. MADIAS: Christensen and Mogensen reported on a small group of patients with incipient diabetic nephropathy (that is, at the microalbuminuric stage) and mild hypertension (baseline of 135/93 mm Hg) who were treated with cardioselective beta blockers and diuretics [91]. Followup for a mean of 3 years revealed that reduction of blood pressure to an average of 125/84 mm Hg was associated with reversal of the pattern of urinary albumin excretion from a mean yearly *increase* of 18% prior to treatment (as judged by, on average, 5 years of observation) to a mean yearly *decrease* of 21% following commencement of antihypertensive therapy. Glomerular filtration rate was supernormal at baseline and remained stable throughout the observation period.

DR. VINCENT CANZANELLO (*Division of Nephrology, New England Medical Center*): In your scheme for determining who will respond to further dietary manipulation, could the use of a converting enzyme inhibitor (CEI) potentially replace diuretic-induced volume depletion?

DR. FINE: It could, only if a CEI has the desired effect on the final measurement, which is a change in protein excretion. There is now evidence that converting enzyme inhibition does reduce proteinuria [92]. You could argue that if a CEI reduces the proteinuria acutely, that this would be appropriate long-term therapy. The problem is that it's entirely possible that any other method of reducing systemic blood pressure might be equally protective. I suppose that what I'm ultimately asking for is for a general approach that looks at the question of whether it is possible, by a small battery of tests, to predict whether a specific therapy will be successful. For the patient, generally a low-protein diet is a major compromise in lifestyle.

Let's try to be scientific and predictive about who should be treated with a given modality. I'm simply raising this question: Can we start looking for these things in humans, rather than rats, so as to decide whether a given patient is going to respond?

DR. MADIAS: In view of the experiment you cited in which administration of sodium bicarbonate apparently reduced the magnitude of the interstitial disease in rats with the remnant kidneys [52], could we imply that—or at least question whether—one of the ways that high-protein diets exert their injurious effects might be through increasing the endogenous acid load?

DR. FINE: That's a good suggestion and, as far as I know, one that has not been addressed. I would caution you, however. For some peculiar reason, in certain rodent species the interstitial disease tends to be more prominent than in others. For instance, this presumably contributes to progressive renal disease in the rabbit with a remnant kidney [4, 8]. Most human renal diseases show both glomerular and interstitial components, but one never knows how much the primary interstitial injury contributes to the decline in function. It is clearly an adaptation that needs to be investigated.

DR. MADIAS: You mentioned that following partial nephrectomy, the glomeruli enlarge. Is there a structural component to this enlargement, or does it merely reflect vascular engorgement secondary to increased blood flow?

DR. FINE: At one time, micropuncture measurements led to the belief that surface area did not increase; today the consensus is that the glomeruli are larger than the controls when studied in vitro. This finding indicates an intrinsic structural enlargement because it occurs in non-perfused glomeruli.

DR. MADIAS: Were various studies that examined the effect of protein restriction on the progression of renal disease controlled for the amount of energy and other nutrients the diet supplied?

DR. FINE: Generally not. Recent animal studies have raised the possibility that carbohydrate restriction preserves the renal parenchyma in rats [93], and no doubt human studies will follow.

DR. DEMETRIOS VLAHAKOS (*Division of Nephrology, New England Medical Center*): You showed us evidence suggesting that hypothyroidism, associated with a decreased metabolic rate, might protect the kidney. Is it possible that the uniqueness of the rat is based on its fast metabolic rate and that, if we wait longer for dogs and humans, we will find the same changes in the kidneys as we found in a shorter period of time in rats?

DR. FINE: I can't answer that question. I didn't address the issue of hypothyroidism other than to show that the protection achieved by dietary phosphate restriction was not mediated by parathyroid hormone. One is left with the conclusion that there might be a role for the thyroid, but there is no reason to suggest that an intrinsic alteration in thyroid function is a primary cause of the problem.

DR. MARY FOSTER (*Division of Nephrology, New England Medical Center*): I am interested in the difference in the rats and other species. In a recent report, Schwartz and colleagues examined epithelial cell function in a remnant kidney model in Sprague-Dawley rats [94]. Examination of the kidneys 6 weeks postoperatively revealed changes in arterioles and glomeruli that resembled changes associated with malignant hypertension. The authors proposed that in this strain of rat, the remnant kidney model is most similar to human malignant nephrosclerosis. They did see some segmental sclerosis at 6 weeks. Has this been seen in other models?

DR. FINE: No, because the other models do not develop the renal lesion. As far as I know, the canine remnant kidney has not been looked at carefully in this regard, and there is no evidence in humans that if you give away one kidney you automatically start developing vascular lesions in the other.

DR. FOSTER: One of their control groups was the spontaneously hypertensive rat (without nephrectomy) that had elevated systemic blood pressures similar to the blood pressures of the nephrectomized Sprague-Dawley rats [93]. The spontaneously hypertensive model did not demonstrate the renal vascular changes.

DR. FINE: You are saying that at the same level of hypertension, vascular changes were seen in the remnant kidney but not in the intact kidney of spontaneously hypertensive rats. This adds further complexity to our understanding of the unique features of the rat remnant kidney and points to decreased glomerular tolerance, perhaps associated with abnormal autoregulation.

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References

1. CHANUTIN A, FERRIS EB: Experimental renal insufficiency produced by partial nephrectomy. I. Control diet. *Arch Intern Med* 49:767–787, 1932
2. SHIMAMURA T, MORRISON AB: A progressive glomerulosclerosis occurring in partial five-sixths nephrectomized rats. *Am J Pathol* 79:95–106, 1975
3. PURKERSON ML, HOFFSTEN PE, KLAHR S: Pathogenesis of the glomerulopathy associated with renal infarction in rats. *Kidney Int* 9:407–417, 1976
4. FINE LG, TRIZNA W, BOURGOIGNIE JJ, BRICKER NS: Functional profile of the uremic nephron. Role of compensatory hypertrophy in the control of fluid reabsorption by the proximal straight tubule. *J Clin Invest* 61:1508–1518, 1978
5. FINE LG, SCHLONDORFF D, TRIZNA W, GILBERT RM, BRICKER NS: Functional profile of the isolated uremic nephron. Impaired water permeability and adenylate cyclase responsiveness of the cortical collecting tubule to vasopressin. *J Clin Invest* 61:1519–1527, 1978
6. FINE LG, YANAGAWA N, SCHULTZE RG, TUCK M, TRIZNA W: Functional profile of the isolated uremic nephron. Potassium adaptation in the rabbit cortical collecting tubule. *J Clin Invest* 64: 1033–1043, 1979
7. TRIZNA W, YANAGAWA N, BAR-KHAYIM Y, HOUSTON B, FINE LG: Functional profile of the isolated uremic nephron. Evidence of proximal tubular "memory" in experimental renal disease. *J Clin Invest* 68:760–767, 1981
8. EDDY AA, FALK RJ, SIBLEY RK, HOSTETTER TH: Subtotal nephrectomy in the rabbit: a model of chronic hypercalcemia, nephrolithiasis, and obstructive nephropathy. *J Lab Clin Med* 107:508–516, 1986
9. WEN SF, WONG NLM, EVANSON RL, LOCKHART EA, DIRKS JH: Micropuncture studies of sodium transport in the remnant kidney of the dog: The effect of graded volume expansion. *J Clin Invest* 52:386–397, 1973
10. ROBERTSON JL, GOLDSCHMIDT M, KRONFELD DS, TOMASZEWSKI JE, HILL GS, BOVEE KC: Long-term renal responses to high dietary protein in dogs with 75% nephrectomy. *Kidney Int* 29:511–519, 1986
11. REISELBACH RE, SHANKEL SW, SLATOPOLSKY E, LUBOWITZ H, BRICKER NS: Glucose titration studies in patients with chronic progressive renal disease. *J Clin Invest* 46:157–163, 1967

12. SLATOPOLSKY E, ELKAN IO, WEERTS C, BRICKER NS: Studies on the characteristics of the control system governing sodium excretion in uremic man. *J Clin Invest* 47:521–530, 1968
13. SLATOPOLSKY E, HOFFSTEN P, PURKERSON M, BRICKER NS: On the influence of extracellular fluid volume expansion and of uremia on bicarbonate reabsorption in man. *J Clin Invest* 49:988–998, 1970
14. OLSON JL, HOSTETTER TH, RENNKE HG, BRENNER BM, VENKATACHALAM MA: Altered glomerular permselectivity and progressive sclerosis following extreme ablation of renal mass. *Kidney Int* 22:112–126, 1982
15. HOSTETTER TH, MEYER TW, RENNKE HG, BRENNER BM: Chronic effects of dietary protein on renal structure and function in the rat with intact and reduced renal mass. *Kidney Int* 30:509–517, 1986
16. RUTHERFORD WE, BORDIER P, MARIE P, HRUSKA K, HARTER H, BLONDIN AJ, HADDAD J, BRICKER N, SLATOPOLSKY E: Phosphate control and 25-hydroxycholecalciferol administration in preventing experimental renal osteodystrophy in the dog. *J Clin Invest* 60: 332–341, 1977
17. HAKIM RM, GOLDSZER RC, BRENNER BM: Hypertension and proteinuria: Long-term sequelae of uninephrectomy in humans. *Kidney Int* 25:930–936, 1984
18. MILLER IL, SUTHANTHIRAN MS, RIGGIO RR, WILLIAMS JJ, RIEHLE RA, VAUGHAN DE, STUBENBORD WT, MOURADIAN J, CHEIGH JS, STENZEL KH: Impact of renal donation: Long-term clinical and biochemical follow-up of living donors in a single center. *Am J Med* 79:201–208, 1986
19. ROBITAILLE P, MONGEAU J, LORTIE L, SINNASSAMY P: Long-term follow-up of patients who underwent unilateral nephrectomy in childhood. *Lancet* 2:1297–1299, 1985
20. BRENNER BM, MEYER TW, HOSTETTER TH: Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med* 307:652–659, 1982
21. HOSTETTER TH, TROY JL, BRENNER BM: Glomerular hemodynamics in experimental diabetes mellitus. *Kidney Int* 19:410–415, 1981
22. BROWN DM, STEFFES MW, THIBERT P, AZAR S, MAUER SM: Glomerular manifestations of diabetes in the BB rat. *Metabolism* 32:131–135, 1983
23. OLIVER J: *Architecture of the Kidney in Chronic Bright's Disease*. New York, Hoeber, 1939
24. ICHIKAWA I, HOYER JR, SEILER MW, BRENNER BM: Mechanism of glomerulotubular balance in the setting of heterogeneous glomerular injury. Preservation of a close functional linkage between individual nephrons and surrounding microvasculature. *J Clin Invest* 69:185–198, 1982
25. FINE LG: The biology of renal hypertrophy. *Kidney Int* 29:619–634, 1986
26. DITZEL J, SCHWARTZ M: Abnormally increased glomerular filtration rate in short-term insulin-treated diabetic subjects. *Diabetes* 16:264–267, 1967
27. MOGENSEN CE: Renal function changes in diabetes. *Diabetes* 25:872–879, 1976
28. CHRISTIANSEN JS, FRANDSEN M, PARVING H-H: The effect of intravenous insulin infusion on kidney function in insulin-dependent diabetes mellitus. *Diabetologia* 20:199–204, 1981
29. BRENNER BM: Nephron adaptation to renal injury or ablation. *Am J Physiol* 249 (Renal Fluid Electrolyte Physiol 18):F324–F337, 1985
30. HOSTETTER TH, OLSON JL, RENNKE HG, VENKATACHALAM MA, BRENNER BM: Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol* 241 (Renal Fluid Electrolyte Physiol 10):F85–F93, 1981
31. NATH KA, KREN SM, HOSTETTER TH: Dietary protein restriction in established renal injury in the rat: Selective role of glomerular capillary pressure in progressive glomerular dysfunction. *J Clin Invest* 78:1199–1205, 1986
32. ANDERSON S, MEYER TW, RENNKE HG, BRENNER BM: Control of glomerular hypertension limits glomerular injury in rats wth reduced renal mass. *J Clin Invest* 76:612–619, 1985
33. ANDERSON S, RENNKE HG, BRENNER BM: Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest* 77:1993–2000, 1986
34. ZATZ R, DUNN BR, MEYER TW, ANDERSON S, RENNKE GH, BRENNER BM: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77:1925–1930, 1986
35. HOSTETTER TH: Human renal response to a meat meal. *Am J Physiol* 250 (Renal Fluid Electrolyte Physiol 19):F613–F618, 1986
36. HARRIS DCH, HAMMOND WS, BURKE TJ, SCHRIER RW: Verapamil protects against progression of experimental chronic renal failure. *Kidney Int* 31:41–46, 1987
37. GOLIGORSKY MS, CHAIMOVITZ C, RAPOPORT J, GOLDSTEIN J, KOL R: Calcium metabolism in uremic nephrocalcinosis: Preventive effect of verapamil. *Kidney Int* 27:774–779, 1985
38. YOSHIDA Y, FOGO A, KIKUCHI T, GLICK A, ICHIKAWA I: Serial micropuncture analyses of the same nephrons in chronic renal diseases: A test for the hyperfiltration theory (*abstract*). *Kidney Int* 31:394, 1987
39. PURKERSON ML, JOIST JH, YATES J, VALDES A, MORRISON A, KLAHR S: Inhibition of thromboxane synthesis ameliorates the progressive kidney disease of rats with subtotal renal ablation. *Proc Natl Acad Sci USA* 82:193–197, 1985
40. BANK N, KLOSE R, AYNEDJIAN HS, NGUYEN D, SABLAY LB: Evidence against increased glomerular pressure initiating diabetic nephropathy. *Kidney Int* 31:898–905, 1987
41. FOGO A, YOSHIDA Y, KIKUCHI T, GLICK A, ICHIKAWA I: Serial micropuncture analysis of the same nephrons in chronic renal diseases (CRD): Studies in two rat models of glomerular sclerosis (GS) (*abstract*). *Kidney Int* 31:384, 1987
42. CASTELLINO P, CODA B, DEFRONZO RA: Effect of amino acid infusion on renal hemodynamics in humans. *Am J Physiol* 251 (Renal Fluid Electrolyte Physiol 20):F132–F140, 1986
43. BOSCH JP, SACCAGGI A, LAUER A, RONCO C, BELLEDONNE M, GLABMAN S: Renal functional reserve in humans: Effect of protein intake on glomerular filtration rate. *Am J Med* 75:943–950, 1983
44. COCHRAN ST, PAGANI JJ, BARBARIC ZL: Nephromegaly in hyperalimentation. *Radiology* 130:603–606, 1979
45. IBELS LS, ALFREY AC, HUFFER WE, CRASWELL PW, WEIL R: Calcification in end-stage kidneys. *Am J Med* 71:33–39, 1981
46. HAUT LL, ALFREY AC, GUGGENHEIM S, BUDDINGTON B, SCHRIER N: Renal toxicity of phosphate in rats. *Kidney Int* 17: 722–731, 1980
47. IBELS LS, ALFREY AC, HAUT LL, HUFFER WE: Preservation of function in experimental renal disease by dietary restriction of phosphate. *N Engl J Med* 298:122–126, 1978
48. KARLINSKY ML, KAUT LL, BUDDINGTON B, SCHRIER NA, ALFREY AC: Preservation of renal function in experimental glomerulonephritis. *Kidney Int* 17:293–302, 1980
49. TOMFORD RC, KARLINSKY ML, BUDDINGTON B, ALFREY AC: Effect of thyroparathyroidectomy and parathyroidectomy on renal function and the nephrotic syndrome in rat nephrotoxic serum nephritis. *J Clin Invest* 68:655–664, 1981
50. CONGER JD, FALK SA: The protective mechanism of thyroidectomy in chronic renal failure (*abstract*). *Kidney Int* 31:381, 1987
51. LUMLERTGUL D, BURKE TJ, GILLUM DM, ALFREY AC, HARRIS DC, HAMMOND WS, SCHRIER RW: Phosphate depletion arrests progression of chronic renal failure independent of protein intake. *Kidney Int* 29:658–666, 1986
52. NATH KA, HOSTETTER MK, HOSTETTER TH: Pathophysiology of chronic tubulo-interstitial disease in rats: Interactions of dietary acid load, ammonia, and complement component C3. *J Clin Invest* 76:667–675, 1985
53. MITCH WE: The influence of the diet on the progression of renal insufficiency. *Annu Rev Med* 35:249–264, 1984
54. EL NAHAS AM, COLES GA: Dietary treatment of chronic renal failure: Ten unanswered questions. *Lancet* 1:597–600, 1986
55. ALVESTRAND A, AHLBERG M, FURST P, BERGSTROM J: Clinical results of long-term treatment with a low protein diet and a new amino acid preparation in patients with chronic uremia. *Clin Nephrol* 19:67–73, 1983
56. BERGSTROM J, ALVESTRAND A, BUCHT H, GUTIERREZ A: Progression of chronic renal failure in man is retarded with more frequent clinical follow-ups and better blood pressure control. *Clin Nephrol* 25:1–6, 1986
57. PARVING HH, ANDERSEN AR, SMIDT UM, OXENBOLL, EDSBERG

B, CHRISTIANSEN JS: Diabetic nephropathy and arterial hypertension. *Diabetologia* 24:10–12, 1983
58. KROLEWSKI AS, WARRAM JH, CHRISTLIEB AR, BUSICK EJ, KAHN CR: The changing natural history of nephropathy in type I diabetes. *Am J Med* 78:785–794, 1985
59. PARVING HH, SMIDT UM, ANDERSEN AR, SVENDSEN PA: Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1:1175–1178, 1983
60. BALDWIN DS, NEUGARTEN J: Blood pressure control and progression of renal insufficiency, in *The Progressive Nature of Renal Disease*, edited by MITCH WE, BRENNER BM, STEIN JH, New York, Churchill Livingstone, 1986, pp 81–110
61. JOHNSON WJ, GOLDSMITH RS, JOWSEY J, ET AL: The influence of maintaining normal serum phosphate and calcium on renal osteodystrophy, in *Vitamin D and Problems Related to Uremic Bone Disease*, edited by NORMAN AW, SCHAEFER K, GRIGIOLEIT HG, VON HERRATH D, RITZ E, New York, Walter de Gruyter, 1975, p 513
62. MASCHIO G, OLDRIZZI L, TESSITORE N, D'ANGELO A, VALVO E, LUPO A, LOSCHIAVO C, FABRIS A, GAMMARO L, RUGIU C, PANZETTA G: Effects of dietary protein and phosphorus restriction on the progression of early renal failure. *Kidney Int* 22:371–376, 1982
63. OLDRIZZI L, RUGIU C, VALVO E, LUPO A, LOSCHIAVO C, GAMMARO L, TESSITORE N, FABRIS A, PANZETTA G, MASCHIO G: Progression of renal failure in patients with renal disease of diverse etiology on protein-restricted diet. *Kidney Int* 27:553–557, 1985
64. EL NAHAS AM, MASTERS-THOMAS A, BRADY SA, FARRINGTON K, WILKINSON V, HILSON AJW, VARGHESE Z, MOORHEAD JF: Selective effect of low protein diets in chronic renal diseases. *Br Med J* 289:1337–1341, 1984
65. ATTMAN PO, BUCHT H, LARSSON O, UDDEBOM G: Protein-reduced diet in diabetic renal failure. *Clin Nephrol* 19:217–220, 1983
66. MITCH WE, WALSER M, STEINMAN TI, HILL S, ZEGER S, TUNGSANGA K: The effect of a keto acid-amino acid supplement to a restricted diet on the progression of chronic renal failure. *N Engl J Med* 311:623–629, 1984
67. ROSMAN JB, MEIJER S, SLUITER WM, TER WEE PM, PIERS-BECHT TPM, DONKER AJM: Prospective randomized trial of early dietary protein restriction in chronic renal failure. *Lancet* 1:1291–1296, 1984
68. ZELLER KR, JACOBSON H, RASKIN P: The effect of dietary protein modification on renal function in diabetic nephropathy. Preliminary report of an ongoing study (*abstract*). *Kidney Int* 31:225, 1987
69. TAGUMA Y, KITAMOTO Y, FUTAKI G, UDEDA H, NONMA H, ISHIZAKI M, TAKAHASHI H, SEKINO H, SASAKI Y: Effect of captopril on heavy proteinuria in azotemic diabetes. *N Engl J Med* 313:1617–1620, 1985
70. HOMMEL E, PARVING HH, MATHIESEN E, EDSBERG B, NIELSEN MD, GIESE J: Effect of captopril on kidney function in insulin-dependent diabetic patients with nephropathy. *Br Med J* 293: 479–480, 1986
71. REAMS GP, BAUER JH: Effect of enalapril in subjects with hypertension associated with moderate to severe renal dysfunction. *Arch Intern Med* 146:2145–2148, 1986
72. DOCCI D, PISTOCCHI E, TURCI F, BALDRATI L: Effect of ibopamine on the progression of chronic renal failure. *Clin Nephrol* 26: 121–124, 1986
73. GOLDBERG LI: Dopamine receptors and hypertension: physiologic and pharmacologic implications. *Am J Med* 77:37–44, 1984
74. OPIE LH, JENNINGS AA: Role of calcium channel blockade in chronic hypertension following successful management of hypertensive emergency. *Am J Med* 81 (suppl 6A):35–42, 1986
75. BARSOTTI G, GIANNONI A, MORELLI E, LAZZERI M, VLAMIS I, BALDI R, GIOVANNETTI S: The decline of renal function slowed by very low phosphorus intake in chronic renal patients following a low nitrogen diet. *Clin Nephrol* 21:54–59, 1984
76. BARRIENTOS A, ARTEAGA J, RODICIO JL, ALVAREZ UDE F, ALCAZAR JM, RUILOPE LM: Role of the control of phosphate in the progression of chronic renal failure. *Miner Electrolyte Metab* 7:127–133, 1982
77. DONADIO JV, ANDERSON CF, MITCHELL JC, HOLLEY KE, ILSTRUP DM, FUSTER V, CHESEBRO JH: Membranoproliferative glomeronephritis: A prospective clinical trial of platelet-inhibitor therapy. *N Engl J Med* 310:1421–1426, 1984
78. ZIMMERMAN SW, MOORTHY AV, DREHER WH, FRIEDMAN A, VARANASI U: Prospective trial of warfarin and dipyridamole in patients with membranoproliferative glomerulonephritis. *Am J Med* 75:920–927, 1983
79. SCHULTZE RG, WEISSER F, BRICKER NS: The influence of uremia on fractional sodium reabsorption by the proximal tubule. *Kidney Int* 2:59–65, 1972
80. CHAN AYM, CHENG ML, KEIL LC, MYERS BD: Functional response of diseased glomeruli to a large protein-meal. *J Clin Invest*, (in press)
81. NEWSON G, SABATINI S, KURTZMAN NA: Renal reserve in normal subjects, transplant donors and patients with nephrotic syndrome (*abstract*). *Kidney Int* 31:211, 1987
82. BIDANI A, SCHWARTZ MM, LEWIS EJ: Renal autoregulation and glomerular vulnerability to hypertensive injury in the remnant kidney model. *Am J Physiol* 252:F1003–F1010, 1987
83. PLOTH DW, ROY RN, HUANG W-C, NAVAR LG: Impaired renal blood flow and cortical pressure autoregulation in contralateral kidneys of Goldblatt hypertensive rats. *Hypertension* 3:67–74, 1981
84. KAYSEN GA, ROSENTHAL C, HUTCHISON FN: Urinary albumin (UalbV) excretion increases in normal rats after increased dietary protein intake without a change in glomerular permeability to neutral dextrans (*abstract*). *Clin Res* 34:600A, 1986
85. SHEMESH O, DEEN WM, BRENNER BM, MCNEELY E, MYERS BD: Effect of colloid volume expansion on glomerular barrier size-selectivity in humans. *Kidney Int* 29:916–923, 1986
86. KAYSEN GA, GAMBERTOGLIO J, JIMINEZ I, JONES H, HUTCHISON FN: Effect of dietary protein intake on albumin homeostasis in nephrotic patients. *Kidney Int* 29:592–577, 1986
87. KIPROV DD, COLVIN RB, MCCLUSKEY RT: Focal and segmental glomerulosclerosis and proteinuria associated with unilateral renal agenesis. *Lab Invest* 46:275–281, 1982
88. MITCH WE, COLLIER VU, WALSER M: Creatinine metabolism in chronic renal failure. *Clin Sci* 58:327–335, 1980
89. STEER KA, SOCHOR M, MCLEAN P: Renal hypertrophy in experimental diabetes. Changes in pentose phosphate pathway activity. *Diabetes* 34:485–490, 1985
90. STEPHAN F, REVILLE P, DE LAHARPE F, KÖLL-BACK M. Impairment of renal compensatory hypertrophy by hypothyroidism in the rat. *Life Sci* 30:623–631, 1982
91. CHRISTENSEN CK, MOGENSEN CE: Effect of antihypertensive treatment on progression of disease in incipient diabetic nephropathy. *Hypertension* 7(II):109–114, 1985
92. HEEG JE, DE JONG PE, VAN DER HEM GK, DE ZEEUW D: Reduction of proteinuria by angiotensin converting enzyme inhibition. *Kidney Int* 32:78–83, 1987
93. KLEINKNECHT C, LAOUARI D, HINGLAIS N, HABIB R, DODU C, LACOUR B, BROYER M: Role of amount and nature of carbohydrates in the course of experimental renal failure. *Kidney Int* 30:687–693, 1986
94. SCHWARTZ MM, BIDANI AK, LEWIS EJ: Glomerular epithelial cell function and pathology following extreme ablation of renal mass. *Am J Pathol* 126:315–324, 1987